NEW YORK HEART ASSOCIATION

PART I—ABSTRACTS OF PAPERS PRESENTED AT THE SCIENTIFIC SESSION ON RESEARCH HELD AT THE NEW YORK ACADEMY OF MEDICINE, APRIL 25, 1966

*Continuous Length-Tension (Starling) Curves of Cat Papillary Muscle**

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Previous studies have shown that diastolic compliance (extensibility) of the intact mammalian heart and isolated tissue preparation is variable. The present experiments were designed to investigate the effects of various inotropic interventions on contraction and diastolic compliance of dynamically changing isolated cardiac muscle.

A system was constructed to monitor muscle length and to control stretch and subsequent relaxation of right ventricular cat papillary muscle in continuous cycles (stretch rate 0.08 to 0.5 mm./min.). During the cycles of stretching and relaxing, various test shocks, including stigmatic and/or field stimulation were applied. Isometric contractions were sensed by a Statham bidirectional transducer and simultaneously recorded at both high and low sensitivities. The continuous length-tension curves obtained were reproducible for any given stretching and stimulation rate during 15- to 45-minute periods. The effects of drugs, metabolic inhibitors and other inotropic interventions were readily visualized over a wide range of resting lengths and force development. This procedure allowed the examination of the effects of inotropic agents on beat-to-beat changes during smooth gradual stretches. This dynamically changing isolated preparation may relate to *in vivo* changes in cardiac fiber length induced, for example, by increments in venous return. The circuitry can also be set to overstretch the muscle (systolic force declines) and thus effects of inotropic agents were examined during "failure."

Results indicate that changes in diastolic compliance can be brought about by paired electrical stimulation, catecholamines and other inotropic interventions during stretch of cardiac muscle. These diastolic compliance changes were particularly noticeable at optimal resting lengths where developed systolic tension was maximal. Endogenous catecholamine release by intense field stimulation also induced increases in diastolic compliance and increments in force development.

The dynamic nature of the experimental conditions of these papillary muscle studies more closely approximates the *in vivo* situation and enhances the value of the conclusions drawn from previous static *in vitro* data.

*These studies were supported in part by a grant from the American Heart Association.

*Use of Reticuloendothelial Phagocytic Function as an Index in Shock Therapy**

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A number of observations from several laboratories have suggested that the capacity to tolerate shock may be associated with an altered phagocytic activity of the elements of the reticuloendothelial system (RES). It has also been reported that experimental exposure to different, apparently unrelated agents such as denatured serum proteins, a variety of colloidal suspensions and certain polysaccharides, leads to an adaptive response in the RES, as manifested by hyperactivity of the phagocytic behavior of these cells. Studies are currently under way, in our laboratory, to ascertain whether spontaneous or drug-induced recovery from experimental shock is accompanied by and correlated with a general stimulation of the phagocytic cells of the RES; these data to serve as diagnostic and therapeutic indices in the therapy of shock. Rats are subjected to a relatively nonlethal (85 per cent survival) form of intestinal ischemia (SMA) shock by temporary ligation of the superior mesenteric artery for 20 minutes. One hour later therapy with vasopressor drugs (norepinephrine, angiotensin or PLV-2, a synthetic analogue of vasopressin) or saline therapy is instituted by i.v. infusion. Phagocytic indices (carbon clearance, K values) are determined at three and 24 hours in untreated and treated survivors. The data, thus far, indicate that RES activity is depressed three hours after SMA shock ($P<0.001$). However, saline- and norepinephrine-treated animals at three hours exhibit almost a 100 per cent increase in phagocytic activity while animals treated with PLV-2 show over a 200 per cent increase in phagocytosis.

All survivors at 24 hours exhibit significant increases in RES activity ($P<0.001$). However, the survivors treated with PLV-2 (which has been reported to exert selective effects on the microcirculation) show the greatest RES stimulation. Over-all these data show that RES phagocytic capacity may correlate as both diagnostic and therapeutic parameter of host responses at a *tissue* level and in addition suggest the potential therapeutic value of exogenous modalities of stimulation of the RES in shock.

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*The Relationship Between the Antiarrhythmic Effect and the Plasma Level of Diphenylhydantoin Sodium (Dilantin)**

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Previous studies have demonstrated that diphenylhydantoin (DPH) can abolish certain arrhythmias. To determine whether the response is related to size of dose or plasma concentration, 100 mg. of DPH were administered intravenously every 5 minutes to 42 patients. The drug was given until: 1) the arrhythmia was abolished; 2) 1000 mg. was administered; or 3) undesirable effects appeared. Blood samples were analyzed by the method of Dill as modified by Kutt.

In all 20 patients with either ventricular premature systoles or ventricular tachycardia, the ectopic activity was abolished when 300 to 500 mg. had been given and when in 75 per cent of the patients the plasma level of DPH reached 10 to 18 μg./ml. In an additional patient with ventricular parasystole DPH was ineffective although the plasma level obtained was similar to that of the other 20 patients.

Three of 4 patients with atrial tachycardia were converted to sinus rhythm with similar dosage and plasma levels as those with ventricular arrhythmias. The fourth patient received 900 mg. of DPH, sustained plasma levels of 20 μg./ml., did not revert to sinus rhythm, and developed somnolence and nystagmus.

Atrial fibrillation, flutter, and premature systoles were not affected in 17 patients with dosage ranging from 500 to 1000 mg. and plasma levels of 18-27 μg./ml. Three fourths of this group experienced either nystagmus, nausea, vomiting, drowsiness, or disorientation when the plasma levels of DPH exceeded 20 μg./ml.

DPH had no effect in 6 patients with nodal premature contractions.

In conclusion, DPH abolished ventricular irritability, excluding a parasystolic focus, usually with plasma levels of 10 to 18 μg.ml. With the exception of atrial tachycardia, it was ineffective in atrial or nodal arrhythmias despite plasma levels of 27 μg./ml. On the basis of these data a method of administration is proposed and a mechanism of action suggested.

*Supported in part by Grant NB-05329 from the National Institutes of Health, Bethesda, Md.
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The Vascular and Extravascular Volumes of the Human Kidney

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In considering a possible role of the kidney in the pathogenesis of essential hypertension, it seemed that alterations in the renal vascular and extravascular volumes might be of importance. In the present work, measurements of these intrarenal volumes have been made in 5 normotensive subjects as a basis for a similar study in essential hypertension. Indicator dilution techniques developed by Chinard in the dog were modified to allow their application in man. Renal volumes of distribution were calculated from the product of the blood flow and mean transit times of 4 indicators: indocyanine green, inulin-carboxyl-C^{14}, creatine, and tritiated water.

Retrograde percutaneous catheterization of the renal artery and vein was performed by the Seldinger technique. A solution containing the four indicators was injected as a bolus into the renal artery, and blood was collected from the renal vein through a densitometer into sampling tubes at 2-second intervals for 80 seconds. The concentration of indocyanine green was recorded by the densitometer; the concentration of each of the other indicators was measured in the collected blood samples. The mean transit times of each indicator were obtained from the concentration curves. Renal blood flow was determined from the indocyanine green, inulin-carboxyl-C^{14} and tritiated water recoveries. The recovery of labeled inulin was corrected for loss in the urine estimated from the concomitantly determined inulin clearance and the clearance and extraction of *p*-aminohippurate.

The distribution volume of indocyanine green averaged 34.8 ± 3.1 ml. and that of tritiated water averaged 152 ± 20 ml. These volumes were interpreted to represent the vascular and total water compartments of the kidney. Labeled inulin and creatinine were used as extracellular indicators and differed in distribution volume by only 7 per cent. The renal extracellular volume determined by inulin averaged 48.8 ± 9.0 ml.

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*The Initiation of Idioventricular Automaticity**

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Ventricular standstill and initiation of an idioventricular rhythm during vagal stimulation proposes the question whether the idioventricular centers (IVC) are transiently suppressed by the vagus or if they were already inhibited prior to the stimulation. Also, the initiation of idioventricular activity after the standstill may be due to changes known to alter the automaticity of Purkinje fibers: 1) distention by the blood flowing into quiescent ventricles; 2) release of catecholamines induced by blood pressure fall or by acetylcholine liberated by the vagus; and 3) changes in potassium outside the cell membrane.

The problem of suppression of IVC and of the onset of idioventricular automaticity was studied in anesthetized dogs with extracorporeal circulation. This technique permitted maintenance of aortic pressure during ventricular standstill, avoidance of ventricular distention, and collection of coronary sinus blood.

The vagus was stimulated for two minutes; during the first minute the ventricles were driven at a rate similar to the control sinus rate. At the end of ventricular drive asystole was still present, suggesting that a fast rate rather than the vagus is the major factor in the suppression of the IVC.

Prevention of ventricular distention did not alter the pattern of escape. Similarly no differences were found whether the blood pressure during vagal stimulation was maintained or allowed to fall.

Coronary sinus potassium was found to decrease consistently during vagal stimulation, and this fall could be prevented by driving the ventricles. These findings indicate that the fall in potassium is rate-dependent and caused by the ventricular arrest. A fall in $[K]_0$ decreases the membrane conductance of Purkinje fibers, and favors the initiation of activity.

In conclusion, the results obtained suggest that: 1) the IVC are suppressed by the relatively fast atrial rate; and 2) a fall in $[K]_0$ plays a role in the initiation of idioventricular activity.

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*Intrarenal Distribution of Blood Flow in the Homotransplanted Dog Kidney**

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Rejection of the homotransplanted kidney may be due largely to a vasculitis especially involving the cortical blood vessels. The intrarenal distribution of blood flow and regional perfusion rates were measured daily in rejecting kidneys, using the method of Thorburn *et al.* (Circ. Res. *13*:270, 1963).

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Krypton 85 dissolved in saline was injected into the renal artery of the homotransplanted kidney through a chronically implanted catheter. Disappearance of radioactivity was monitored with an external scintillation counter. The resultant multiexponential decay curve could best be graphically resolved by the method of serial back subtraction into four major components: Cortical, outer medullary, inner medullary, and perirenal and perihilar fat. As rejection progresses the cortical flow rate often falls slowly but, more importantly, the per cent of the initial counts going to the cortex falls progressively. It falls greatly just before or at the time the kidney becomes anuric. Outer medullary flow decreases more gradually and somewhat later than cortical flow, while inner medullary and hilar fat flows remain unchanged. Flow rates in renal autotransplants remained essentially normal. In the treated animal (azathiprine and prednisolene) flow rates and the pattern of distribution could be returned to normal after periods of rejection. Histology in the untreated group revealed changes typical of rejected renal homotransplants. Less pronounced changes were seen in the treated animal.

The krypton 85 method is applicable to humans and it is possible that serial measurements of the intrarenal distribution of blood flow in human renal homotransplants may provide useful clinical information.

*Association of S-T Depression with Myocardial Potassium Loss During Coronary Insufficiency**

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Depression of the S-T segment of the electrocardiogram is usually evident during angina pectoris. A similar, but less marked S-T depression is seen after digitalis administration. S-T depression may occur in clinical hypokalemia, and this has been duplicated in animals by perfusion of the heart with a potassium-free solution. Efflux of potassium from the myocardium following digitalization has been demonstrated in man and experimental animals. The present study was done to determine whether potassium loss from the myocardium accompanied depression of the S-T segment during experimental coronary insufficiency. In 9 experiments, ischemia of the entire left ventricle was produced by gradual reduction in left main flow until the following events occurred simultaneously: rise of left atrial pressure, maximal myocardial oxygen extraction, minimal coronary vascular resistance and myocardial lactate production. At this point, evidence of potassium efflux from the myocardium was present with coronary A-V difference averaging minus 0.5 mEq./l. (range -0.1 to -1.0). Control values averaged +0.1 mEq./l. (range -0.1 to -0.2). Simultaneously, a flat depression of the S-T segment of the electrocardiogram (lead II) occurred averaging 3.3 mm. (range 1.3 to 9.5). In 2 experiments, *p*H measurements during S-T depression revealed a coronary A-V difference averaging 0.15 units (range 0.0 to 0.02). It is concluded that during coronary insufficiency potassium is lost from the myocardium and that this potassium loss is associated with depression of the S-T segment. Furthermore, a possible cause of this S-T depression is suggested by the loss of potassium ion observed during experimental myocardial ischemia, digitalis administration and hypokalemia.

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NEW YORK HEART ASSOCIATION

PART II—ABSTRACTS OF PAPERS SUBMITTED FOR PRESENTATION AT THE SCIENTIFIC SESSION ON RESEARCH, HELD AT THE NEW YORK ACADEMY OF MEDICINE, APRIL 25, 1966

*Total Prosthetic Heart**

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A mechanical, intrapericardial total heart prosthesis is reported. Consisting of flat right ventricle, cylindrical left ventricle, and four valves (two membrane- or butterfly-type inlets and two tricuspid semilunar-type or butterfly-type outlets), it has a combined Silastic connection to the atria and separate short connectors to the aorta and pulmonary artery. Fiberglas resin coated with Silastic form the rigid outer housing of the ventricles, and Silastic the inner pumping chamber. Driven by compressed air in an open loop system, the duration of diastole, systole, air pressure, and suction are each independently adjustable. Implantation in dogs weighing approximately 30 kg. requires from 75 to 105 minutes of extracorporeal circulation time using a homologous lung as an oxygenator.

The heart has a capacity of 40 ml. on either side and fits securely inside the pericardium. Combined artificial atria have been provided with a ridged Silastic closed sponge along the long suture line to avert bleeding between tissue and the plastic material at the site of anastomosis. When the pericardium is sutured together to the right atrial anastomosis, hemostasis, and reinforcement are provided. Cardiac pressure in each chamber can be monitored continuously. In the present system, pressures and suctions in the exhaust line and optimal conditions of air have been determined. Further investigation is under way of the relations between ratio of systole and diastole, pressure, and its form. The dog that survived the longest—27 hours—was able to stand and walk.

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*Effect of Hypervolemia on Cardiac Output and Renal Blood Flow in Ganglionic Blockade**

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Previous studies have shown that drug-induced hypotension reduces the blood loss from the severed saphenous artery of the dog to 8 per cent of the control, but that it also depresses cardiac output (CO) and renal blood flow (RBF). In an effort to correct the depression of CO and RBF, we studied the effects of hypervolemia during maintained hypotension.

Cardiac output, directly measured renal blood flow and blood volume were determined, and aortic and superior vena caval pressures were recorded. These values were measured during a control period, after the animal had been made hypotensive by the intravenous administration of trimethaphan camsylate, and then after the hypotensive animal had been made hypervolemic by the transfusion of autologous blood (25 to 35 per cent of calculated blood volume). The results obtained are shown:

A mean reduction in blood pressure of 54.8 per cent caused a 35.8 per cent mean reduction in cardiac output and a 44 per cent mean reduction in renal blood flow. While hypotension was maintained autologous transfusion of 25 to 35 per cent of the animal's blood volume raised both the cardiac output and the renal blood flow to control levels.

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	Mean cardiac output cc./min.	*Mean RBF/g./min.*	*Mean blood-volume*
Control	2102 cc.	270 g.	2.56 l.
Hypotensive "normovolemic"	1243 cc.	146 g.	2.19 l.
Hypotensive hypervolemic	2100 cc.	246 g.	3.03 l.

*Myocardial Assist: Comparison of Left Heart Bypass with Counterpulsation**

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We have devised a system for comparing left heart bypass with counterpulsation in the same animal under virtually identical conditions. We have studied the effects of these systems on the work of the heart as measured by the tension-time index.

Eleven mongrel dogs were studied. Electrocardiogram, aortic arch pressure, left ventricular pressure, pulsating chamber pressure, and cardiac output were recorded. Left heart bypass was performed without thoracotomy, using the cannula described by Senning *et al.*** Counterpulsation was performed using a newly devised pulsating chamber driven by compressed air and synchronized to the electrocardiogram. The same chamber converted pulseless to pulsatile flow in studies of left heart bypass. Pressures were adjusted only by adding or removing blood.

Tension-time index of controls (without assist) fell an average of 15.5 per cent with each 25 mm./Hg reduction in mean pressure between 150 and 50 mm./Hg. A parallel decrease was noted in cardiac output. Therefore assisted studies were compared only at similar mean pressures. Counterpulsation produced a decrease in tension-time index of 10 to 20 per cent at all mean pressure levels studied. Whereas left heart bypass produced reductions in tension-time index of 12 to 26 per cent at mean aortic pressure of 150 mm./Hg, a far greater effect was noted at lower than normal mean pressures. At 100 mm./Hg. left heart bypass produced a 38 to 44 per cent decrease and at 75 mm./Hg a 39 to 52.7 per cent decrease was noted.

Left heart bypass was significantly more effective in reducing tension-time index at all levels below 150 mm./Hg. Slight differences were noted between pulseless and pulsatile forms of left heart bypass.

Changes in aortic mean pressure alter myocardial work as measured by tension-time index and may also affect organ perfusion. Therefore regulation of this *parameter is necessary for objective evaluation of systems of myocardial augmentation.*

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**Senning, A., Dennis, C., Hall, D. P. and Moreno, J. A. Left atrial cannulation without thoracotomy for total left heart bypass, *Acta Chir. Scand. 123*:267, 1962.

*Endotoxin and Myocardial Contractility**

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Results obtained in the usual studies carried out in the intact dog on the effect of *Escherichia coli* endotoxin on myocardial contractility are affected by multiple factors inherent in the use of the experimental model; these factors include blood volume, blood pressure, heart rate, *p*H, pCO_2, pO_2—as well as the possible effect of the endotoxin. By utilizing total cardiopulmonary bypass and the isovolumic left ventricle it is possible to control these multiple factors which affect results and thus one is able to assess the specific effect of the endotoxin on myocardial contractility.

The effect of *E. coli* endotoxin on myocardial contractility in the isovolumic left ventricle was studied during 2 hours of total cardiopulmonary bypass in each of 8 dogs. Our results indicate that *E. coli* endotoxin impairs neither left ventricular pressure development in the isovolumic left ventricle nor the maximum rate of left ventricular pressure rise (dp/dt). The specific findings cited above have import for all investigators working on the problem of endotoxic shock.

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*The Auxiliary Ventricle: Function During Experimental Heart Failure**

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The hemodynamic effects of our U-shaped auxiliary ventricle were studied in 25 dogs with heart failure induced by bleeding, left coronary ligation, mitral insufficiency and coronary microspheric embolization to simulate the hemodynamic alterations encountered in clinical left ventricular failure.

Before induction of failure in these dogs, the device reduced left ventricular pressure by 30 per cent, and increased coronary flow by 20 per cent with no significant change in aortic flow. Results with the unit operated in dogs in heart failure (indicated by a decrease in systolic pressure, increases in left ventricular diastolic pressure and left atrial pressure) were as follows:

1) Peak atrial pressure exceeded the natural systolic peak.

2) Left ventricular pressure was reduced by an average of 47 per cent.

3) Left ventricular diastolic pressure returned to normal.

4) Left atrial pressure was reduced by 40 per cent.

5) Aortic flow was increased by 50 per cent.

In some cases, these improvements led to recovery with the dogs' condition remaining stable until sacrifice.

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*Response of Myocardial Fiber Length to Left Heart Bypass**

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Consistent reduction in myocardial oxygen uptake occurs with left heart bypass of as little as 15 per cent of the cardiac output, but the left ventricular tension-time index (T.T.I.) does not drop until bypass is nearly total. The slope of systolic rising pressure curve (dp/dt) likewise does not change significantly. However, in accordance with the law of Laplace, myocardial fiber shortening may reduce the oxygen consumption by decreasing the radius of curvature of the left ventricle.

Left ventricular end-diastolic and end-systolic fiber length were measured in 9 dogs with the chest open, both by two-plane cinematography and by attachment of Whitney mercury strain gauges to the epicardium. High-speed cinematography permitted later projection or microscopic micrometry for measurements between markers or anatomical landmarks on the epicardium. Left atriam to femoral artery bypass was employed. Multiple experiments in each preparation revealed significant reduction in end-diastolic fiber length, approximately 7 per cent in total cardiac bypass, ($p<0.001$) and 3 per cent in partial (50 per cent total) bypass, ($p<0.002$) regardless of which method was used for measurement. The reduced ventricular filling during bypass was not associated with comparable shortening of end-systolic fiber length; thus the degree of myocardial fiber contraction in each stroke decreased as more blood was bypassed. This is in contrast to what was observed during hypovolemic shock, in which the amplitude of myocardial contraction increased.

It is suggested that these factors may play a role in the reduction of myocardial oxygen uptake on degrees of left heart bypass insufficient to reduce the tension-time index.

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*Mechanisms of Atrial Arrhythmias Due to Digitalis**

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The mechanisms responsible for supraventricular arrhythmias caused by digitalis have not been defined in terms of its effects on electrical activity of the SA node (SAN) and specialized atrial fibers (SAF). To this end, we have studied the effects of ouabain (10^{-6} to 10^{-7}M) on transmembrane potentials of atrium, SAN, sinoatrial ring bundle (SARB), crista terminalis (CT) and Bachmann's bundle (BB) in isolated preparations of rabbit and puppy heart perfused with modified Tyrode solution.

Ouabain first depressed and then enhanced phase 4 depolarization, and thus

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automaticity, of cells in the SAN, the CT and SARB. Initial depression of automaticity was abolished by atropine. Heterotopic automatic foci developed most often in the CT and SARB in the vicinity of the coronary sinus; such foci ultimately suppressed the SAN pacemaker. Occasionally, multiple independent heterotopic foci coexisted. Conduction disturbances, including decremental conduction, were common and often caused failure of conduction from automatic foci to atrial muscle. In some experiments conduction from an ectopic pacemaker was maintained along the CT and BB at a time when atrial muscle fibres were inexcitable. Reentrant rhythms also were common, particularly during the early stages of the development of digitalis toxicity in nonatropinized preparations.

These studies provide electrophysiological corroboration of the vagomimetic effects of digitalis as well as the occurrence of arrhythmias due to both reentry and enhanced phase 4 depolarization of SAF in digitalis excess. They define the sites of the heterotopic foci and delineate the effects of digitalis on the SAN. The differences in response of ordinary and specialized atrial fibers lend support to the concept of a specialized atrial conduction system and provide one explanation for the development of reentry.

*Effects of Dilantin and Digitalis on Potassium Uptake and Egress in the Dog Myocardium**

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Similarities between the effects of i.v. dilantin and i.v. potassium in alleviation of various cardiac arrhythmias have been reported. The hypothesis that dilantin might exert its antiarrhythmic action by means of alteration of potassium ion fluxes across the myocardial cell was examined. The effects of dilantin on the canine myocardial K uptake and content were determined *in vitro*. Fresh myocardial slices were incubated in buffered Krebs-Ringer solution, *pH* 7.4, containing glucose and K^{42}, under a 95 per cent O_2 atmosphere for 90 minutes. To one fourth of these slices was added 5×10^{-5} *M* ouabain, to one fourth was added 2×10^{-4} *M dilantin,* to one fourth was added both dilantin and ouabain, and one fourth served as controls. After the incubation and 2 washings, the K^{42} and total K content of the slices, media and muscle was determined.

The muscle and media total K determinaitons suggest that a large potassium egress occurs in the controls. The addition of ouabain results in even greater K losses. Dilantin did not alter the K egress in the controls nor the total K loss in the ouabain-treated slices. K^{42} uptakes were greatly reduced with digitalis but were unaffected by dilantin alone. Dilantin did not affect the K^{42} uptakes in the digitalis-treated slices. Therefore, in the isolated, noncontractile heart muscle *in vitro, large* concentrations of dilantin did not affect the K^{42} uptakes nor the magnitude of K egress in both the control and the ouabain-treated slices.

*Supported by grants from the National Institutes of Health (AM-2828) and from the American Heart Association.
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*Analysis of Arrhythmias During Open Heart Surgery by the Use of Epicardial Leads**

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The purpose of this study was to determine the usefulness of epicardial electrograms in the interpretation of arrhythmias during open heart surgery. An acrylic plaque electrode containing five silver contacts 2 to 4 mm. apart was sutured to the epicardial surface of the right atrium and a ventricle in 15 patients undergoing open heart surgery. A close bipolar atrial and ventricular electrogram, a unipolar electrogram and a lead-2 electrocardiogram were simultaneously monitored throughout each surgical procedure. All records were taken on a multichannel oscilloscopic photographic recorder.

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The following arrhythmias were delineated by the epicardial electrogram and frequently could not be determined by the lead 2 electrocardiogram:

Sinus tachycardia with first degree block, atrial standstill, Wenckebach cycles, A-V dissociation with and without captured beats, concealed conduction of the A-V node, nodal rhythm with retrograde atrial activation, and ventricular tachycardia with retrograde atrial activation.

This study demonstrates the efficacy of direct recordings from the heart in the interpretation of arrhythmias. Therefore, we now routinely obtain intra-atrial electrograms in the immediate postoperative period by placing a recording electrode in the standard central venous catheter.

*Orthotopic Transplantation of Canine Cadaver Hearts**

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The previously reported surgical technique developed in this laboratory for orthotopic heart transplantation in puppies under profound hypothermia has proved successful. These achievements with direct transplants of fresh hearts led to investigations of a similar procedure utilizing canine hearts stored for varying periods of time.

Technique: After heparinization, asphyxia was induced by ether: when blood pressure reached zero the donors were left at room temperature for varying times from 7 to 60 minutes to simulate time intervals that would be appropriate clinically. Three procedures were used in 19 puppies: direct

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transplants, short- and long-term perfusion of the isolated heart.

Results: A) direct transplants: in a series of 9 dogs, we found: donor hearts anoxiated for periods longer than 15 minutes were unsuccessful when transplanted; *B*) no improvement in 3 transplants following 30-minute perfusion with oxygenated blood of hearts anoxiated 30 and 45 minutes; *C*) best results were achieved with those transplantations in 7 dogs which followed 2 hours of isolated perfusion: of these, 2, who had received hearts from donors dead 45 minutes, died within 24 hours from irreversible myocardial damage. Of the remaining 5, recipients of hearts anoxic for 30 minutes, 2 with successful transplants were technical failures and 3 survived, 4, 5, and 14 days respectively.

Conclusion: The outside time limit before onset of irreversible myocardial damage in the cadaver heart appears to be between 30 and 45 minutes. EKG study of the isolated hearts during the two-hour perfusion period gives information concerning viability of the transplant thus diminishing operative risk.

*The Echocardiographic Diagnosis of Pericardial Effusion**

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The ultrasound reflection technique (echocardiography) is compared with the isotope photoscanning method in the differentiation of pericardial effusion from myocardial dilatation. A series of 25 patients with enlarged cardiac silouettes was studied, 13 of whom had pericardial effusions. Echocardiography correlated satisfactorily with photoscanning only in the group of patients with effusions, although 2 false-negative echo studies were obtained. Seven false-positive echocardiograms were obtained from the group of patients without pericardial effusions.

It is suggested that the echocardiographic method may not detect effusions in the anterior pericardial space, that pleural effusions may produce false-positive echo records, and that false-positive results may be obtained in the absence of any other evidence of effusion. Whether this is an artefact or a function of the sensitivity of the method is unclear.

It is concluded that the echo method is a safe and easy technique which can be regarded only as an adjunct to the other diagnostic methods available for the confirmation of pericardial effusion.

Acid-Base, Electrolyte and Renal Functional Alterations During and Following High-Flow Hemodilution Perfusion

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Hemodilution perfusion has reduced the incidence of complications following total cardiopulmonary bypass. However, studies on three groups of patients (41), each receiving a different hemodiluted perfusate, have shown that these perfusates, in themselves, cause changes in acid-base balance, body fluid and electrolyte composition, and renal function. Each perfusate consisted of 50 per cent ACD blood and 50 per cent diluent. The diluent was dextrose/Ringer's/albumin solution in two perfusates and homologous plasma in the third. THAM, in three varying amounts, was added to buffer the perfusates. The following measurements were made before, during and after perfusion: *p*H, pCO_2, bicarbonate concentration, base excess; GFR, Uosm, TcH_2O; plasma and urine Na, K and Cl. Perfusion time averaged two hours. During perfusion, acid-base data (corrected for hypothermic temperatures) showed isohydric values (*p*H 7.40) where larger total amounts of THAM were infused and respiratory acidosis where less buffer was employed. Urine flow rates were increased during and immediately after perfusion secondary to a glucose/THAM solute diuresis. Despite the high urine flow, GFR and renal concentrating capacity (Uosm and TcH_2O) were markedly depressed but returned to normal postperfusion. A marked chloruresis was observed during and immediately after perfusion. This was attributed to the large THAM excretion and was associated with a variable postoperative hypochloremia. In addition, a kaluresis ensued postperfusion. Analysis of these data has resulted in a change in postoperative fluid and electrolyte management following hemodilution perfusion. Solutions relatively high in Na, K, and Cl content have been employed postoperatively even in the presence of antecedent congestive heart failure.

Effect of Dialysate Temperature and Flow Rate on Peritoneal Clearance

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Using a repeated puncture technique with commercially available Dianeal solution and Y-tubing, repeated peritoneal dialyses on the same patient over a period of 16 months were studied to observe the effect of dialysate temperature change and flow rate on peritoneal urea nitrogen clearance.

Peritoneal exchanges were studied under the following conditions:

1) Flow of 2 liters of 20° C. fluid every 2 hours.

2) Flow of 2 liters of 37° C. fluid every 2 hours.

3) Flow of 2 liters of 20° C. fluid every hour.

4) Flow of 2 liters of 37° C. fluid every hour.

5) Repeated inflow and outflow of 2 liters

of 37° C. fluid without pause.

6) Repeated inflow and outflow of 2 liters of 37° C. fluid with pumped outflow.

7) Repeated 1-liter and 2-liter inflows at a standard dialysate rate.

The following results were obtained:

1) Warming solutions accelerated the exchange of substances between the peritoneal fluid and blood.

2) At a standard dialysis rate, a 2-liter inflow is more effective than a 1-liter inflow.

3) As the dialyzing rate increases, the clearance increases. The clearance increases up to a flow rate of 3.3 l./hr., at which the urea nitrogen clearance is 20.8 ml./min. There is a slight drop in clearance with a secondary increase starting at a dialyzed volume of 4.8 l./hr. and continuing to increase to our maximal dialysate rate of 8.5 l./hr. at which the urea nitrogen clearance is 26.9 ml./min. This is in contradiction to the drop in clearance after a dialyzed volume of 3.5 l./hr. shown by Boen but is in agreement with the continued increase in clearance shown by the automatic peritoneal dialysis machine.

4) The most practical, efficient peritoneal dialysis style is the rapid inflow and outflow of 2-l. exchanges at 37° C. without a pause.

*Hepatic Function in Uremia**

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Destruction of liver parenchyma by neoplasm, hepatitis, or nutritional cirrhosis is frequently accompanied by serious impairment of renal function, the so-called "hepato-renal syndrome." In this study, the influence of advanced renal disease on several measures of hepatic synthetic and detoxification processes was assessed.

The following chemical determinations were obtained in duplicate from 23 patients whose endogenous creatinine clearance was less than 4 ml. per minute: thymol turbidity, cephalin flocculation, serum bilirubin, serum proteinelectrophoresis, serum retention of bromosulfophthalein, serum alkaline phosphatase, serum iron and iron binding capacity, and four-hour oral glucose tolerance test.

Of 15 patients supported by twice-weekly hemodialysis (Group I) the diagnoses were chronic glomerulonephritis, 11; chronic pyelonephritis, 3; hereditary interstitial nephritis, 1. Elevated gamma globulin fractions were present in 12 patients, abnormal cephalin flocculation in 11 patients, slight BSP retention in 5 patients and elevated alkaline phosphatase activities in 5 patients in Group I. The diagnoses of 8 patients receiving conservative management for renal failure (Group II) were chronic glomerulonephritis, 7, and chronic pyelonephritis, 1. Similar chemical abnormalities were found in Group II. Despite the abnormalities in chemical determinations discovered in both groups, only one patient had hepatomegaly and none were icteric. Hepatic function is preserved to a considerable degree in uremic patients.

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*Clinical and Experimental Experience with Gas Endarterectomy**

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The utilization of a gas bolus to dissect the diseased inner layers of blood vessel from the more normal outer adventitia has now been used as an adjunct to endarterectomy in over 150 vessels in 40 patients. A 26-gauge needle connected to a CO_2 tank by a sterile plastic tube is inserted subadventitially into the vessel in question. The tank is turned on to a flow of 20 liters per minute, and the gas is seen and felt to dissect the length of the vessel. The technique has obviated the need for long arterotomies and tedious dissection and thus permits endarterectomy over long reaches of vessels from aorta to distal popliteal, in times which approach those necessary to do a shunt or graft over similar distances. Initially it made femoral-popliteal shunts more rapid by speeding the local endarterectomy at points of graft insertion. Following understanding of potential usefulness, the technique has made possible rapid femoral-distal popliteal and posterior-tibial endarterectomy, in patients with at least one major vessel run-off at the knee, with consistent clinical success (90 per cent in 25 cases).

The technique develops a more satisfactory and consistent endarterectomy plane usually outside the outer layer of media in extremely diseased vessels—so that only adventitia per se remains. In spite of this, no aneurysm formation has been observed.

The technique which has now afforded some success in the peripheral vascular tree is being investigated as to its applicability in coronary artery disease. Over 50 atherosclerotic cadaver hearts have been studied with the intent of revascularizing either the right or left coronary tree. *In vivo* experiments in the dog have been undertaken to study the effects of a carbon dioxide bolus introduced directly into the coronary arterial system. The results of these investigations lead us to believe that many of the most important objections to coronary endarterectomy can be overcome.

*The Effects of Variations of Pulmonary Blood Flow Utilizing an Artificial Right Ventricle**

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Over the past five years work in this laboratory has progressed toward the development of an implantable cardiac substitute. This device has been used in dogs or as a uni- or bilateral ventricular substitute to evaluate cardiovascular function. Difficulties encountered in our laboratory, as well as by other investigators engaged in similar projects, made it necessary to study specifically fundamental physiological questions of the pulmonary and systemic blood flow. This present study was undertaken to resolve problems encountered in the right heart bypass.

In dogs the right ventricle was replaced by an artificial ventricle composed of a

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**Lewis Cass Ledyard Fellow in Cardiovascular Surgery.

rigid outer chamber and a compressible inner chamber containing appropriate caged-ball valves to provide unidirectional flow. The ventricle is actuated by a hydraulic pump which permits stroke volume, rate and duration of systolic and diastolic phase to be varied independently. Animals were perfused with blood at 37° C. and ventilated by positive pressure. The blood pressure, stroke volume, and heart rate were varied, and pO_2 pCO_2, and pH were measured. The average contact time of red cells in the alveoli was determined. The relationship between the contact time of red cells, pulmonary artery pressure, blood flow, and ventilation was studied. Results indicate that when the average contact time of red cells in alveoli was shortened by raising pulmonary arterial pressure, by changing the stroke volume or the heart rate, the pO_2 and pH dropped while the pCO_2 rose. Arterial O_2 tension (pO_2) was found closely correlated with pulmonary arterial pressure and dependent on stroke volume and heart rate.

*Reciprocal Changes in Serum Cholesterol and Transaminase: A Manifestation of Drug-Induced Pyridoxine Antagonism**

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This study was based on the following premises. First, the monamine oxidase inhibitors have certain common features which suggest that they might be pyridoxine antagonists: some have a pyridine ring, some have a hydrazine group, and most occasionally cause neuropathies which are said to respond to pyridoxine administration. Second, pyridoxine is an essential coenzyme for transaminase reactions. Third, pyridoxine deficiency in animals often results in reduced liver and serum transaminase activity and hyperlipemia. Accordingly, various monamine oxidase inhibitors were administered in ordinary doses to over fifty hypertensive and/or neurotic patients over a period of several months, and multiple determinations of the serum cholesterol and glutamic-oxaloacetic transaminase activity were made before, during, and after drug therapy. Four to ten determinations were made in each of these periods, and the results averaged in order to minimize spontaneous variations and technical errors. Conclusions were based on comparisons of these averages.

After several weeks, those patients who showed baseline transaminase levels of 9 to 14 units tended to develop a rise in their transaminase and a fall in their cholesterol; those who showed baseline transaminase levels of 19 units or greater tended to develop a fall in their transaminase and a rise in their cholesterol; and those who showed baseline levels of 15 to 18 units usually failed to show any change at all. The changes in serum transaminase and cholesterol were reversible by pyridoxine administration in about half the cases, so that pyridoxine antagonism appears to be the mechanism responsible for the serum changes. Why some patients developed changes in one direction while others developed changes in the opposite direction—yet both the result of the same fundamental mechanism—is not clear. Inhibition of monamine oxidase activity does not seem to be necessary for the effect, for drugs (such as isoniazid) with little or no such action can elicit an identical phenomenon.

The role of pyridoxine-dependent enzymes in the regulation of cholesterol metabolism seems to be a promising field for future studies.

*Prevalence of Bacteriuria in Patients Receiving Chronic Hemodialysis**

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Among the factors said to predispose to bacteriuria are azotemia and low urine flow rates. Intermittent hemodialysis may prolong the lives of patients with severe renal failure. During the course of chronic dialysis therapy, the patient remains azotemic and develops a progressive decrease in urine production. Fifteen patients, 11 men and 4 women, aged 16 to 56 years, are currently receiving twice-weekly overnight hemodialysis. The duration of dialysis therapy varied from 2 to 26 months at the time of study. The patients' diagnoses were chronic glomerulonephritis, 11; chronic pyelonephritis, 3; and hereditary interstitial nephritis, 1. Daily urine volumes were less than 100 ml. for 8 patients, between 100 and 400 ml. for 6 patients, and over 400 ml. for one patient. Two patients were totally anuric and were excluded from the study.

First morning mid-stream urine samples were collected after cleansing the urethral meatus and the surrounding skin with benzalkonium chloride (Zephiran) 1:1000. Three urine samples were obtained from each patient on separate days. The urine specimens were diluted in molten soytrypticase broth and cultured in pour plates as described by Kass. Significant bacteriuria was defined as the presence of 100,000 or more bacteria per ml. of undiluted urine.

Only one patient, a 32-year-old woman, with a historical and histologic diagnosis of chronic pyelonephritis, had significant bacteriuria with each of three cultures yielding more than 100,000 of *Escherichia coli, Streptococcus viridans* or *Aerobacter aerogenes.* One of 3 urine cultures obtained from a 19-year-old man with hereditary nephritis yielded a colony count greater than 100,000 of *Pseudomonas aeruginosa.* All other cultures were either sterile, 22, or had insignificant colony counts, 13. It is concluded that the combination of parenchymal renal damage and low urine flow rates does not necessarily lead to sustained urinary tract infection.

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*Myocardial Contractility, Myocardial Infarction and Isuprel**

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By utilizing the isovolumic left ventricle and total cardiopulmonary bypass it is possible to control multiple variables which affect myocardial contractility and thus to assess the effect of a specific agent or of a specific condition under study. A study designed to determine the effects of: 1) heart rate, and 2) isuprel on contractility of the acutely infarcted left ventricle was carried out on 11 dogs. The heart was paced by an electrode sutured to the epicardial surface of the left ventricle after complete heart block was obtained by placing a suture ligature around the His bundle. Controlled pacing excluded the chronotropic effect of isuprel, which would in itself alter dp/dt, and permitted study of the inotropic effect alone. Acute infarction was produced by constricting the anterior descending branch of the left coronary artery just below the origin of the anterior septal branch. Results of this study demonstrate 1) that dp/dt rose wth increases in heart rate before and after acute infarction; and 2) that the use of isuprel results in further increases in dp/dt at all rates studied before and after acute infarction. The infarcted area failed to contract with or without isuprel and bulged outward during systole. Since the chronotropic and peripheral effects of isuprel—as well as multiple other variables affecting myocardial contractility—were controlled in this study, these results reflect a more valid appraisal of the ability of isuprel to increase myocardial contractility following acute myocardial infarction.

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*Transvenous Catheter Pacing: Analysis of Functional Motion Stress**

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Since the advent of transvenous catheter electrode cardiac pacing, multiple areas of endocardial electrode placement and venous sites of catheter insertion have been employed. It is the purpose of this presentation to demonstrate which of several modes of implanted or exteriorized catheter pacing are stable, and which are unreliable and even hazardous. Cine cardiograms taken with various type catheters inserted from the cephalic, external jugular, brachial, and femoral veins, and placed in the RV apex or RV mid-outflow positions, will be shown. Th eeffects of arm, neck, shoulder, and leg motion upon local catheter stresses and endocardial positions are readily apparent.

It can be concluded that external jugular and cephalic installations of braided wire catheters located in the mid-RV outflow and coiled spring catheter located in the RV apex are relatively safe if positioned properly. Installations from other sites are subject to motion displacement and may be dangerous.

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*The Cardiovascular Response to Epinephrine and Phentolamine Following Hemorrhage**

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The effect of epinephrine and phentolamine on the cardiac output and peripheral vasculature was studied in dogs following hemorrhage.

Ten dogs weighing 14 to 30 kg. were anesthetized with i.v. Na-pentobarbital, 30 mg./kg., intubated and placed on controlled ventilation. Lumen catheters were positioned in the left ventricle, aorta and right atrium. Left ventricular and aortic pressures, cardiac outputs done in duplicate by the dye dilution technique, and A-V differences were obtained during a control period and 1½ to 2 hours after acute hemorrhage of 30 per cent of the blood volume. In the post-hemorrhagic state, in 5 experiments hemodynamic measurements were made during an i.v. infusion of epinephrine, 3.5 μg./kg/min. before and 20 minutes after the i.v. administration of phentolamine, 0.5 mg./kg., and in other 5 experiments hemodynamic measurements were made 20 minutes after the administration of phentolamine and during the infusion of epinephrine after alpha blockade. All records were taken on a multichannel oscilloscopic photographic recorder.

Hemorrhage decreased the cardiac output 55 per cent and increased the peripheral resistance 100 per cent. In the post-hemorrhagic state it was found that: 1) epinephrine increased the cardiac output 30 per cent and decreased the peripheral resistance 25 per cent; 2) phentolamine increased the cardiac output 8 per cent and decreased the peripheral resistance 20 per cent; and 3) epinephrine with phentolamine increased the cardiac output 120 per cent and decreased the peripheral resistance 70 per cent. The A-V differences confirmed the changes in cardiac output.

In the posthemorrhagic state, epinephrine with phentolamine restored the cardiac output to control levels while the peripheral resistance was reduced to 50 per cent of control. There was an inverse relationship between cardiac output and peripheral resistance, and no direct relationship between cardiac output and mean arterial pressure.

This study demonstrates that beta-adrenergic stimulation with adrenergic blockade through the concomitant use of epinephrine and phentolamine will markedly increase the cardiac output in the post-hemorrhagic state.

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*Hemodialysis for Chronic Renal Failure**

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Eleven men and 4 women, ranging in age from 16 to 56 years, with terminal oliguric renal failure, have been maintained as active outpatients with intermittent hemodialysis comprising a total experience of 14 patient-years. Endogenous creatinine clearances were less than 4 ml./min. when treatment was begun. Seven patients excrete 100 to 400 ml. of urine per day, and the rest excrete less than 100 ml. of urine per day. Twice weekly, overnight, 12- to 16-hour dialyses are performed with Kiil dialyzers, supplied by an automated, electronically monitored, central dialysis delivery system in a 14-bed unit. Dialyses are conducted and monitored by nurses, under the supervision of on-call physicians. Teflon-silastic arteriovenous shunts provide repeated and safe access to the patients' circulating blood.

Diastolic blood pressures are maintained at levels of 80 to 100 mm./Hg in 14 of the 15 patients by restriction of dietary sodium to 400 to 600 mg. per day and removal of excess fluid and sodium during dialyses. Antihypertensive medication has not been routinely used. Predialysis blood urea nitrogen and creatinine concentrations range from 60 to 100 mg. per cent and 7 to 14 mg. per cent respectively, while postdialysis values are 15 to 30 mg. per cent and 4 to 6 mg. per cent. Three patients have asymptomatic osteodystrophy manifested by persistent and otherwise unexplained serum alkaline phosphatase elevations. One patient has been partially incapacitated by renal rickets and secondary hyperparathyroidism. The anemia of uremia has not been corrected by dialysis, and blood transfusion requirements range from 0.5 to 4 units per month. Three patients developed asymptomatic anicteric hepatitis and two patients were symptomatic, with icteric hepatitis. Apparently stable, subclinical peripheral neuropathy is manifested by abnormal nerve conduction velocities in 14 patients. Serious psychiatric problems have not been encountered.

Thirteen patients have been fully rehabilitated to gainful employment, full-time student activities or household duties. Two patients are partially rehabilitated. There have been no deaths. Intermittent hemodialysis is an effective method of life prolongation and rehabilitation of selected patients with renal failure.

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*Depression of Ventricular Automaticity by Electrical Stimulation**

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Posttachycardia depression of the primary pacemaker is an important cause of Adams-Stokes attacks. To investigate the mechanism by which prolonged asystole may follow sudden termination of an ectopic tachycardia, trained unanesthetized dogs with surgically induced complete heart block were paced at varying rates and durations via implanted ventricular electrodes.

Abrupt cessation of ventricular stimulation is followed by asystole for several seconds. The slowed heart rate then gradually increases, may briefly exceed control for a few seconds, but then remains depressed for 1 to 2 minutes. Increasing the rate or duration of stimulation prolongs post-pacing depresssion. Maximum depression occurs after 30 to 60 seconds and remains unchanged with 4½ hours of continuous pacing. During a series of brief pacing periods (e.g. 10 seconds) postpacing asystole progressively lengthens, demonstrating that depressor effects are additive. Recovery is enhanced by lengthening the interval between pacing periods. The depressant effect of paired stimuli causing a single ventricular contraction at 90/minute is significantly more pronounced than single stimuli inducing the same ventricular rate (p. <0.001), but similar to that following 180 equally spaced stimuli per minute. This suggests that the frequency of electrical, not mechanical events, influences the degree of depression. Variations in stimulus intensity and duration do not influence postpacing depression. Subthreshold stimuli have no effect on the idioventricular rate. Postpacing depression is inversely rated to the resting idioventricular rate prior to stimulation. Propranolol increases and *N*-methyl atropine and isoproterenol decrease post-stimulation depression.

These data indicate that repetitive electrical stimulation depresses ventricular automaticity. Depression gradually accumulates during ventricular pacing and is progressively overcome when stimulation ceases. The neurohumoral transmitters apparently influence this phenomenon.

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*Cardiovascular Effects of Adrenergic Blockade and Acute Hemorrhage in Splenectomized Dogs**

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The effects of adrenergic blockade on cardiodynamics and the hepatic and renal fraction of the cardiac output were determined in splenectomized dogs under chloralose anesthesia. ECG, right atrial and femoral arterial pressures, left ventricular pressure and its first derivative (dp/dt) were recorded simultaneously. Cardiac output (CO), hepatic and renal flows (HBF and RBF) and glomerular filtration rate (GFR) were determined by multiple-indicator-dilution techniques during control period, after drug injection and after 10 ml./kg. hemorrhage in 4 groups of dogs: 6 saline controls (C) and 6 each receiving trimethaphan (ARF), phenoxybenzamine (DBZ) and propranolol (PRP). Ventricular stroke volume (SV) and work (W) were calculated. Changes after blockade are shown in the table.

After acute hemorrhage notable change were limited to PRP group as compared to C group, and consisted of marked decreases in CO, dp/dt and HR; RBF and GFR were maintained.

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	CO	*W*	*SV*	*dp/dt*	*Art. P*	*HR*	*HBF*	*RBF*	*GFR*
C	u	u	↓	u	u	u	↓	u	u
ARF	↓	↓	↓	↓	↓↓	u	u	u	↓
DBZ	u	↓	u	↓	↓↓	↑	↓	u	u
PRP	↓	↓↓	↓	↓	↓	↓	u	u	u